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Prospective Article

Dendritic cells and TNF-Related apoptosis inducing ligand (TRAIL) represent new possibilities for sepsis treatment

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Abstract

Sepsis refers to a generalized inflammatory response of the organism to an infection or to bacterial products in circulation, rather than the development of an infection *per se*. Despite recent advances in clinical practice and overall medical care, sepsis remains a great health care problem and is still the most common cause of death in critically ill patients with infection. We suppose that during the course of sepsis the expression of TRAIL in different organs correlates with acute mortality and further development of multiple organ dysfunction syndrome (MODS). It is expected that dendritic cells (DCs) might become targets for apoptotic processes in a result of elevated TRAIL expression. This hypothesis is a bias for detailed investigations for *in vivo* studies in animal models and for *in vitro* studies of septic patients.

Background

The imbalance between pro-inflammatory and anti-inflammatory cytokine activities favors the induction of acute and chronic inflammation. Many of the components of the innate immune response that normally ensure host defenses against infection can cause cell and tissue damage and can lead to multiple organ failure, the clinical hallmark of sepsis. The cells of the innate immune system play a crucial part in the initiation and subsequent direction of adaptive immune responses, as well as participating in the removal of pathogens [1,2]. These processes are related to the production of cytokines, which participate in nearly every biological process although they are not specific for only one tissue and most cells in the body synthesize them [3]. Moreover, in cell cultures several cytokines trigger a biological response although a visible band on gel electrophoresis was not found [4]. In sepsis the immune system goes into overdrive, and the mediators that are released into the blood to combat the infection, trigger widespread inflammation in the entire body [5-7]. Because of the high mortality of sepsis, many efforts have been made to reveal how the host protection is deregulated. As a result, new data have been accumulated about basic principles underlying bacterial-host interactions [8]. Although sepsis is a deadly, acute disease, survivors also suffer long-term consequences. Clinical data underscore subsequent high mortality rates associated with patients who are long-term survivors of the acute septic episode . This makes evident the need for new therapies with fewer side effects [9].

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Dendritic cells originate from bone marrow stem cells and home to all tissues *via* the blood stream where they develope and differentiate. In response to endogenous danger signals or microbial antigens, DCs maturate and migrate into the T cell area of lymphoid tissues. They also activate effector T lymphocytes and induce Treg proliferation, thus determining the type of immune responses toward inflammation or anti-inflammation [10]. During the process of maturation, DCs upregulate the presentation of cell surface proteins involved in T cell priming, including MHC, CD40, CD80, and CD86. During the development of sepsis DCs are involved in the induction of apoptosis, reactive oxygen species generation and activation of the Wnt signaling pathway [11]. The membrane bound CD14 act as a pattern recognition receptor of the innate immune response enabling cells to produce inflammatory cytokines against bacterial infections [12,13]. It is known that Toll-like receptors (TLR) family play a cruncial role in the clearance of pathogen by promoting proinflammatory response. However, the activation of TLR during this process requires the interaction with dendritic cell coreceptor CD14 which can amplify the inflammatory signal primed by bacterial pathogen [14]. Thus, CD14 might be a potential target for skewing Th1 response in sepsis [15]. Although both the inflammatory and anti-inflammatory cytokine levels are elevated in patients with severe sepsis, the anti-inflammatory cytokine IL-10 is the main predictor of severity and fatal outcome [16,17]. Available data reported that septic DCs exhibit an aberrant cytokine secretion pattern, in which levels of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-12 are significantly suppressed, while anti-inflammatory cytokines, such as TGF-β and IL-10 are enhanced [18]. Numerous studies suggest that apoptotic death of immune cells plays a vital role in contributing to the immune hyporesponsiveness and organ injury during sepsis [3,19-20]. In the early stage of cecal ligation and puncture sepsis, a significant increase of apoptotic and dead DCs is found in mesenteric and inguinal nodes [21-23].

More recent data indicate that substantial heterogeneity exists in septic patients, either being immuno-stimulated, whereas others appear suppressed [24-25]. Cellular changes are also relevant with the theme of heterogeneity. Some cells are too activated for an extended time such as neutrophils. Other cellular changes become accelerated including cell apoptosis which may play a crucial role in the pathophysiology of sepsis. A lot of investigations have been focused on lymphocyte apoptosis as a potential factor in the immunosuppression and mortality of sepsis [26]. Cell death is induced through two major signaling extrinsic and intrinsic pathways. In the extrinsic pathway, also termed as death receptor pathway, external proteins bind to cell-surface receptors that subsequently induce apoptosis [27]. A family of membrane TNF receptors (TNF-Rs), including TNFR1, Fas, DR3, DR4, DR5, and DR6 belongs to this signaling pathway. They are characterized with an extracellular cysteine-rich domain, needed for ligand binding, and an intracellular death domain, needed for apoptotic signal transduction. The ligand for these death receptors are TNF-α, Fas ligand (FasL), TRAIL (TNF-related apoptosis inducing ligand), and Apo3 ligand. Binding of TRAIL to its receptor might express immunosuppressive or immunoregulatory functions, as well as might play proviral or antiviral, and tumour immunosurveillance roles. The induction of apoptosis is a result of the interaction of TRAIL with two death receptors TRAIL-R1 (DR4) or TRAIL-R2 (DR5). Thereby, the receptors are trimerised and the death-inducing signaling complex is formed. In mice, there is only one full-length receptor mDR5, which is equally homologous to human DR4 and DR5. Also, two murine decoy receptors mDcTRAILR1 and mDcTRAILR2 which lack a death domain have been identified [28]. Both TRAIL and TRAIL-Rs are constitutively expressed by various cells of the immune system, including natural killer cells, activated T cells, natural killer T cells, dendritic cells and monocyte/macrophages and are up-regulated upon cell activation [29]. It is considered that TRAIL has the ability to induce apoptosis preferentially in transformed cells, while in nontransformed cells the actions of TRAIL are less investigated. Studies in animals and humans with infection proved the complicated character of this condition. TRAIL can provoke an immune suppression through inducing a massive

death of different immune cell populations [30]. If a new infection challenge appears, the TRAIL-dependent suppressive mechanisms will prevent pathogen clearance and the organism is sensitive to the infection. Blocking TRAIL through systemic anti-TRAIL antibody administration, prevents the pathogen-induced immune suppression, keeping entire T cell-mediated immune function to clear the infection, and increase the survival. Apoptosis is responsible for the physiological removal of damaged or senescent cells, in mature tissues, as well as in tissue remodeling during development. By counterbalancing mitosis, apoptosis is important to keep tissue homeostasis during normal cell turnover, and to control tissue growth and regeneration. Apoptosis-induced loss of lymphocytes may be one of the key triggers of sepsis. The accompanying immunosuppression is thought to be mediated by two major pathways: direct apoptosis of key effector cells or indirect but apoptosis-induced anergy in surviving macrophages and dendritic cells [31]. Taken together, multiorgan apoptosis can occur during sepsis and appears to contribute to septic morbidity. Localized in the plasma membrane, TRAIL-R1 and TRAIL-R2, induce apoptosis and non-apoptotic signaling when crosslinked by the ligand TRAIL or by agonistic receptor-specific antibodies.

Conclusion

It has been assumed that the loss of DCs is partly dependent on cell apoptosis, so the methods that can inhibit the apoptosis are thought to be beneficial for sepsis. We hypothesize that TRAIL neutralization can be a new approach for limiting DC apoptosis. Many questions pertinent to apoptosis in septic patients have yet to be answered. The cells or tissues that become apoptotic are probably much more heterogeneous than the existing evidences suggest. On the basis of the source or site of septic insult, new patterns of apoptotic depletion may be discovered. Further investigations are needed to define the cell populations expressing TRAIL consistently and to accumulate more data on the role of decoy receptors as TRAIL-R3 and TRAIL-R4 that are supposed to counteract TRAIL-R1 and TRAIL-R2.

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